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Application Number	09/714,882
Filing Date	11/16/00
First Named Inventor	Turner
Group Art Unit	1646
Examiner Name	E. B. O'Hara
Total Number of Pages in This Submission: 15	Attorney Docket Number: LEX-0091-USA

ENCLOSURES *(check all that apply)*

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Lexicon Genetics Incorporated Lance K. Ishimoto Reg. No. 41,866
Signature	Kurt Ishimoto by Peter G. Sefarian Reg No 40162
Date	March 5, 2004

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express mail label EV322477444US addressed to: Commissioner for Patents, MS Appeal Brief - Patents, P.O. Box 1450, Alexandria, VA 22313 on: March 5, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	*Turner et al.*	Group Art Unit:	1646
Application No.:	09/714,882	Examiner:	O'Hara, E.B.
Filed:	November 16, 2000		
Title:	Human *Notch* Ligand Proteins and Polynucleotides Encoding the Same	Atty. Docket No.	LEX-0091-USA

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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REPLY BRIEF

Sir:

Appellants hereby submit an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Examiner's Answer mailed on January 5, 2004 which is due on March 5, 2004. This Reply Brief is thus timely submitted.

Appellants believe no additional fees are due in connection with this Reply Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

Appellants agree with the Examiner's assertion that "A statement identifying the real party in interest is contained in the brief" (Examiner's Answer at page 2).

II. RELATED APPEALS AND INTERFERENCES

Appellants disagree with the Examiner's Answer which states that the brief does not contain a statement identifying the related appeals and interferences....

Appellants note that the brief contained the following statement at the bottom of page 1, "Appellants know of no related appeals or interferences."

III. STATUS OF THE CLAIMS

Appellants agree with the Examiner's assertion that "The statement of the status of the claims contained in the brief is correct" (Examiner's Answer at page 2).

IV. STATUS OF THE AMENDMENTS

Appellants agree with the Examiner's assertion that "The appellant's statement of the status of amendments after final rejection contained in the brief is correct" (Examiner's Answer at page 2).

V. SUMMARY OF THE INVENTION

Appellants essentially agree with the Examiner's assertion that "The summary of invention contained in the brief is essentially correct, except that the asserted utilities for the claimed invention are currently being disputed." (Examiner's Answer at page 2).

VI. ISSUES ON APPEAL

Appellants agree with the Examiner's assertion that "The appellant's statement of the issues in the brief is correct." (Examiner's Answer at page 2).

VII. GROUPING OF THE CLAIMS

Appellants agree with the Examiner's assertion that "The appellant's provide a statement in the brief that the claims stand or fall together."(Examiner's Answer at page 2).

VIII. CLAIMS APPEALED

Appellants agree with the Examiner's assertion that "The copy of the appealed claims contained in the Appendix to the brief is correct" (Examiner's Answer at page 2).

IX. PRIOR ART OF RECORD

Appellants essentially agree with the Examiner's assertion as to the art previously presented by the Examiner in this case with the exception of the omission of Bowie *et al*, 1990, Science **247**:1306-1310.

X. ARGUMENT

A. Do Claims 1-8 Lack a Patentable Utility?

Appellants do not wish to restate all of the arguments presented in the Appeal Brief concerning the Examiner's allegation that claims 1-8 lack a patentable utility, and instead incorporate the entirety of Section VIII(A) of the Appeal Brief at this point herein by reference. However, Appellants feel the need to specifically address several of the arguments presented in the Examiner's Answer in some detail for the record.

Appellants do not wish to restate all of the arguments presented in the Appeal Brief concerning the Examiner's allegation that claims 1-8 lack a patentable utility, and instead incorporate the entirety of Section VIII(A) of the Appeal Brief at this point herein by reference. However, Appellants feel the need to specifically address several of the arguments presented in the Examiner's Answer in some detail for the record.

The Examiner is attempting to reject the present application based on the position that the claimed invention lacks a specific and substantial utility for has been made. Appellants strongly disagree. The biological significance and function of *Notch* signaling pathway and *Notch* ligands is supported by many scientific publications, among others, the two review articles that were cited by the Examiner in the Advisory Action, which clearly support Applicant's assertions made in the specification (page 14, lines 12-23). Also, in Section 2 of the specification Appellants taught that "SEL-1 proteins are negative regulators of *Notch* family receptors. *Notch* receptors and their associated signaling pathways have been associated with development, apoptosis, neuron growth and maintenance. The utility of *Notch* proteins and ligands are therefore clearly well-known to those of skill in the art. The Examiner appears to accept as credible Appellants assertions regarding the identity of the protein encoded by the sequences of the present invention is SEL-1 like. Further the Examiner's answer, on line 6 of page 9, admits that these proteins are probably in the *Notch* family. The Examiner's Answer also notes on page 10, lines 11-12 that the "specific activities associated with Notch family members are dependent upon the protein and the cell or tissue it is expressed in." The protein encoded by the sequences of the present invention are expressed in human testis, the site

of significant cell division and apoptosis, further supporting the credibility of Appellants' assertion.

Appellants submit that the legal test for utility is an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable.

> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

Therefore, as Appellants have made the credible assertion that the sequences of the present invention encode a *Notch* ligand protein and the utility of *Notch* proteins and ligands are clearly well-known to those of skill in the art. Thus, the logical conclusion is that the sequences of present invention also have patentable utility and rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112, first paragraph utility rejection should be overruled.

The Examiner's Answer also reiterates the Examiner's previously stated position that sequence homology and the relationship between structure and function is not generally accepted by those of skill in the art. In support of this position the Examiners Answer goes on to describe again several contrarian articles that have been both previously presented and rebutted by the Appellant. None of these articles constitute direct evidence that Appellants' assertion that the sequences of the present invention encode a *Notch* ligand is not credible as none of the cited articles describe the protein of the present invention.

The Examiner's Answer first reiterates an article cited in the Final Action by Yan *et al.* ("Yan"; 2000, Science 290:523-527). However, this paper cites only <u>one</u> example, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact <u>related</u> (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based <u>solely on sequence similarity</u> (Yan at page 523).

Thus, Yan is hardly indicative of a high level of uncertainty in assigning function based on sequence, for that is the approach chosen by the authors and it thus also does not support the alleged lack of utility of the sequences of the present invention.

The Examiner's Answer next reiterates an article by Ji, *et al.* ("Ji"; 1998, J. Biol. Chem. *273*:17299-17302) as teaching that structural homology alone is not a good predictor of function. But an exact quote from Ji, completely undermines this argument: "a substantial degree of amino acid homology is found between members of a particular subfamily, but comparisons between subfamilies show significantly less or no similarity" (Ji, at 17299, first paragraph, emphasis added). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that subfamily.

In summary a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the staring point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (multiple B.S. and Ph.D. level scientists).

As stated previously, while there may not be a 100% consensus within the scientific community regarding prediction of protein function from homology information, this is not unusual nor is it indicative of a general lack of consensus. These articles are just examples of the few contrarian (erroneously described as spurious) articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. A few rare exceptions do not a rule make.

One form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the results of a recent search of the NCBI-NLM-NIH public scientific database "PubMed" using the term "bioinformatics" which resulted in 5,548 different scientific publications

(these will not be provided to avoid burdening the USPTOs scanning group). If bioinformatic information is not useful in predicting protein function from structural homology information, why are so many publications reporting the results of its use?

A second form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the fact that many scientists, corporations and institutions elect to allocate significant proportions of their limited resources for access to private bioinformatic systems and databases. Thus, it would appear obvious that those of skill in the art value and accept the results of bioinformatic analysis for they are willing to pay dearly for access to such information.

A third, an perhaps most persuasive form of evidence supporting the position that bioinformatic information is recognized to be of value by those of skill in the art is the issuance of multiple US patents regarding bioinformatic prediction and methods for doing the same (see for example, U.S. Patent Nos. 6,229,911, 6,567,540, 6,615,141, 6,631,331, 6,651,008, 6,677,114, these patents will not be provided to avoid burdening the USPTOs scanning group). Of particular interest might be U.S. Patent No. 6,466,874, one of whose claims reads "A method of identifying proteins as functionally linked, the method comprising comparing sequences to find homologous functional domains." Why would a U.S. Patent have issued on a method of carrying out an analysis that is without utility, because it is not accepted by those of skill in the art as a credible method of predicting protein function from structural homology information?

Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be believable. Appellants submit that the overwhelming majority of those of skill in the relevant art would believe prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools. Clearly the several forms of evidence presented, and certainly the issuance of U.S. Patents suggest that those of skill in the art recognize the utility of bioinformatic analysis and its credibility in assessing structure function relationships. Thus the vast majority of those of skill in the art would believe that Appellants sequence is a *Notch* ligand (erroneously noted to be a CUB domain, due to clerical error), SEL-1 like protein.

Given the legal test for utility simply involves an assessment of whether those skilled in the art would

find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Examiner's Answer also discounts several arguments concerning the utilities of the sequences of the present invention since other nucleic acid sequences can be used in a similar fashion. In addition to the detailed arguments presented by Appellants in the Appeal Brief with regard to each of these asserted utilities, Appellants once again point out that these arguments are completely rebuffed by the Federal Circuit's holding in *Carl Zeiss, supra* ("[A]n invention need not be the best or only way to accomplish a certain result").

The main argument concerning these utilities is that of use of the specific sequences on DNA chips or to map the human chromosome or as polymorphic markers is that since potentially other nucleic acid sequences can be used to map the human chromosome, for forensic identification or on DNA chips, these utilities do not represent specific or substantial utilities.

The main argument concerning this utility is that as other nucleic acid sequences can be used to map the human chromosome, this does not represent a specific or substantial utility. Appellants believe that the mapping of one of the relatively few transcribed, spliced and expressed human genes encoding a novel *Notch* ligand to a specific location in the human chromosome provides very useful information. For example, the mapping of the relatively few expressed human genes to a particular chromosome has long been a recognized method of identifying a gene's role in a particular disease. Furthermore, the mapping of the human chromosome is a project of such widely recognized importance by those of skill in the art and even lay people, that both the U.S. government and private corporations have dedicated millions of dollars to such a project. One must ask, if the mapping of human chromosomes is a throw away utility then why

has the U.S. government elected to spend so many of its limited taxpayer dollars on this project?

With regard to forensic identification, what could be more real world. Naturally occurring genetic polymorphisms such as those described in the present specification are both the basis of, and critical to, *inter alia*, forensic genetic analysis and genetic analysis intended to resolve issues of identity and paternity. Therefore, Applicants find this position difficult to comprehend, given that the results of identity and paternal analysis often have great emotional and substantial economic impact. These sound like very substantial and real world utilities. What could be more substantial and real world than the loss of an individual's freedom through incarceration and in some cases even the loss of life through execution? Yet forensic analysis is often used to convict or acquit in many cases. Both paternal and forensic genetic analysis is based on the use of identified polymorphisms. This is a well known and generally accepted by those of skill in the art, who would readily recognize the utility and value of any identified polymorphism. Without identified polymorphisms, one would not be able to carry out such forensic or paternal analyses. The present application has identified just such essential polymorphisms within the sequences of the present invention.

The Examiner's Answer assumes, correctly, that other expressed human nucleic acid sequences that contains a naturally occurring polymorphism could potentially be used in forensic analysis, in human paternity determinations or human population migration determinations, and then falsely concludes that therefore such utilities are generic and lack substantial and specific utility. Applicants submit that until a specific polymorphic marker is actually described it has very limited utility in forensic analysis. Put another way, simply because there is a likelihood, even a significant likelihood, that a particular nucleic acid sequence might contain a polymorphism and thus be useful in forensic analysis, until such a specific polymorphism is actually identified and described, such a likelihood is meaningless. The Examiner is perhaps attempting to use the information presented for the first time by Appellants in the instant specification as hindsight verification that the presently claimed sequence would be expected to have polymorphic markers. Such a hindsight analysis based on Applicants discovery would not be proper.

While taking the position that because there are other objects having the same utility, that utility has been rendered generic and therefore is not specific and substantial, the Examiner's Answer (on page 21-22) states that patents are issued on batteries, golf balls and tires by the USPTO because the invention in

each patent has a specific and substantial utility. What is the specific utility of a golf ball if it is not for use in the game of golf? The use of a golf ball in the game of golf would, following this line of logic, of course be generic as any golf ball can be used in the game of golf. The Examiner's Answer states that the distinction between the present invention and a golf ball is that "a golf ball can be used" and presumably the Examiner feels that the present invention cannot be used. Applicants firmly disagree with the presumption that those of skill in the art would not know how to use the present invention. In fact those of skill in the art would readily know how to make and use the present invention in a multitude of ways, several of were described in the specification of the present case.

The sequences of the present invention provide a specific marker of the gene encoding a novel human *Notch* ligand that is expressed in some human tissues and not others. Thus, these sequences provide a unique identifier of the corresponding gene in the human genome. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as they represent expressed human gene sequences with a defined tissue expression pattern. While, the Examiner agrees that such "DNA chips" have utility, as evidenced by issued U.S. Patents, she argues that specific sequences which define a specific gene that is actually expressed and clearly increases the utility of such a patented invention do not have utility. It must again be noted that this position runs counter to the position regarding golf balls.

Finally, while accepting the Examiner's right to withhold comment and with full recognition of the fact that all patent applications are examined on their own merits and that the prosecution of one patent does not effect the prosecution of another patent, *In re Wertheim,* 541 F.2d 257, 264, 191 USPQ 90, 97 (CCPA 1976), however the issue at hand in one of whether the fact that patents have issued recognizing the utility of a class of molecules does this confers a statutory precedent of patentability to a broad class of compositions. Thus, there remains a lingering issue regarding due process and equitable treatment under the law. While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for

patent examination set forth by the USPTO. Furthermore, Appellants respectfully submit that it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. Given the rapid pace of development in the biotechnology arts, it is difficult for the Appellants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than prior inventions that were issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, it stands to reason that Appellants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record in the Appeal Brief. Thus, holding Appellants invention to a different standard of utility appears inconsistent and inequitable, such a judgement being arbitrary and capricious, a violation of due process and equal protection under the law.

For each of the foregoing reasons, as well as the reasons set forth in the Appeal Brief, Appellants submit that the rejection of claims 1-8 under 35 U.S.C. § 101 should be overruled.

B. Are Claims 1-8 Unusable Due to a Lack of Patentable Utility?

Regarding the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility, Appellants submit that as claims 1-8 have been shown to have "a specific, substantial, and credible utility", as detailed in Section X(A) above, as well as Section VIII(A) of the Appeal Brief, the present rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, must be overruled.

XI. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-8 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

March 5, 2004
Date

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Agent For Appellants

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